CASE REPORT

Multifocal intraductal papillary mucinous neoplasm of the pancreas-A case report

Kun-Chun Chiang, Jun Te Hsu, Huang-Yang Chen, Shyh Chuan Jwo, Tsann-Long Hwang, Yi-Yin Jan, Chun-Nan Yeh

Kun-Chun Chiang, Jun Te Hsu, Huang-Yang Chen, Shyh Chuan Jwo, Tsann-Long Hwang, Yi-Yin Jan, Chun-Nan Yeh, Department of Surgery Chang Gung Memorial Hospital, Chang Gung University, 5, Fu-Hsing Street, Kwei-Shan, Taoyuan, Taiwan, 333, China
Author contributions: Chiang KC wrote the manuscript; Hsu JT, Chen HY and Jwo SC provided the data and contributed to the manuscript writing; Hwang TL, Jan YY, Yeh CN supervised and approved the final manuscript.
Correspondence to: Dr. Chun-Nan Yeh, Department of General Surgery, 5, Fu-Hsing Street, Kwei-Shan, Taoyuan, Taiwan, 333, China. ycn@adm.cgmh.org.tw
Telephone: +886-3-3281200 Fax: +886-3-3285818
Received: September 9,2008 Revised: December 17, 2008
Accepted: December 24, 2008
Published online: February 7, 2009

Abstract

Cystic neoplasms of the pancreas are relatively rare, comprising 10 percent of pancreatic cysts and only 1 percent of pancreatic cancers. Cystic neoplasms include mucinous cystic neoplasms, serous cystadenomas, papillary cystic tumors, cystic islet cell tumors and intraductal papillary mucinous neoplasms of the pancreas (IPMNs). IPMN was first described in 1982. It has been most commonly described in 60 to 70 years old males, and represents a relatively "new" but increasingly recognized disease. The improvement and widespread use of modern imaging equipments and heightened awareness of physicians contribute to the increasing incidence of IPMN. The majority of IPMNs are located in the pancreatic head (75%) while the rest involves the body/tail regions. Multifocal IPMNs have been hypothesized, but the true presence of multifocality is unknown. Here we present a 72-year-old male diagnosed with IPMN (carcinoma *in situ*) in the pancreatic head and a branch duct type IPMN (duct atypia) in the pancreatic body and tail. The patient underwent a Whipple intervention and a distal pancreatectomy. A three-year disease-free survival has been observed so far.

INTRODUCTION

Cystic neoplasms of the pancreas are relatively rare, comprising 10 percent of pancreatic cysts and only 1 percent of pancreatic cancers. Cystic neoplasms encompasses mucinous cystic neoplasms, serous cystadenomas, papillary cystic tumors, cystic islet cell tumors and intraductal papillary mucinous neoplasms of the pancreas (IPMNs)[1,2].

IPMN was first described in Japan in 1982, when four patients, diagnosed with pancreatic carcinoma with favorable outcomes, were reported sharing three distinct clinical features: dilated main pancreatic duct, patulous ampullary orifice and mucus secretion[3]. Since then, several reports have described mucus-producing pancreatic tumors with different stages of carcinogenesis, referred to by a variety of names[4-10], but mostly as mucinous ductal cancers. IPMN has very clear malignant potential and exhibits a broad histological spectrum, ranging from minimal mucinous hyperplasia to adenoma to invasive carcinoma[11-13].

The criteria used to classify IPMNs and to discriminate them from other mucin-producing cystic neoplasms of the pancreas have been established by the WHO in 1996[14]. The WHO gave a clear definition for IPMNs as intraductal mucin-producing neoplasms with tall, columnar, mucin-containing epithelium, with or without papillary projections. This type of neoplasm involves the main pancreatic duct and/or major side branches.

The majority of IPMNs are located in the pancreatic head (75%), while the rest involves the body/tail regions[15]. Multifocal neoplasms have been hypothesized[15], but the real prevalence of multifocality is unknown. Here, we present a 72-year-old male diagnosed with non-invasive
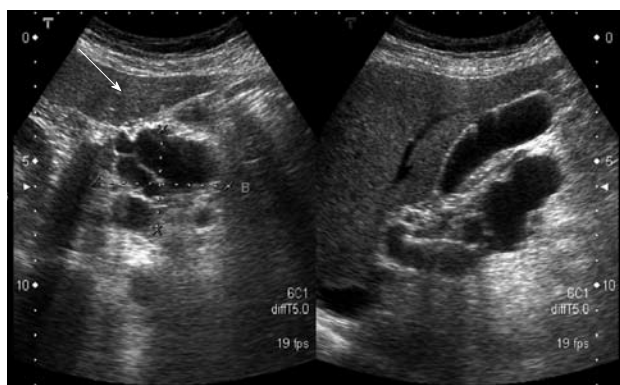
Figure 1 Abdominal ultrosonograpy showing multiple cystic tumors over the pancreatic head area with P-duct dilatation.
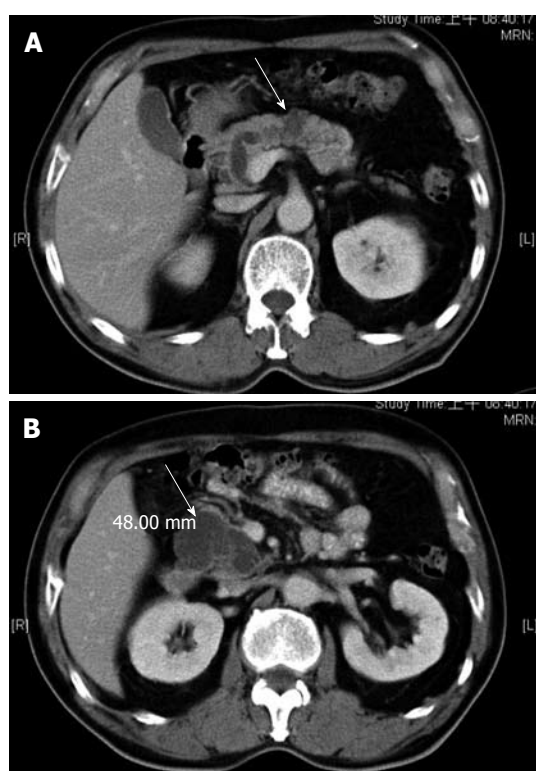

Figure 2 Abdominal computed tomography showing pancreatic head and body cystic tumors (arrow) with no evidence of regional lymphadenopathy or distant metastases.

Figure 3 The endoscopic ultrasonogaphy showed that the papilla of Vater was grossly normal without mucin discharge. However, a cystic tumor (arrow) measuring 4.0 cm x 4.2 cm in size was seen over the pancreatic head. The lining of cysts showed no definite projectile mass and the pancreatic duct was dilated about 0.6 cm in the head and 0.4 cm in the body and tail area.

mixed type IPMN (carcinoma *in situ*) in the pancreatic head together with a branch duct type IPMN (duct atypia) in the pancreatic body and tail.

CASE REPORT

A 72 years old male presented in 2005 with abdominal fullness after meals, general weakness, and body weight loss of about 2-3 kg occurred during the previous 3 mo. He had had diabetes and hypertension under regular medical control for the past 8 years. He was first admitted as outpatient, and an upper panendoscopy was performed, which showed chronic duodenal ulcer and gastric erosions. Antacids were prescribed but symptoms were not relieved.
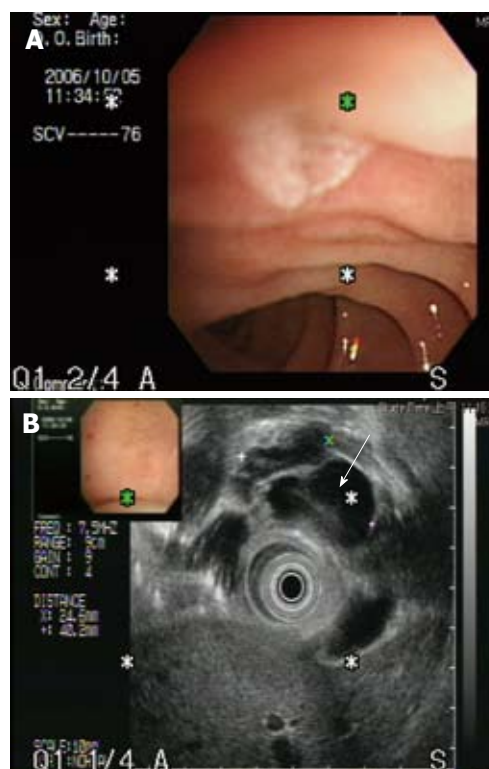
Abdominal ultrosonography was then carried out (Figure 1) and a pancreatic head cystic tumor with pancreatic duct dilatation (0.75 cm) was found. He was then hospitalized for further treatment. The physical examination revealed a soft abdomen without palpable mass. No lymphadenopathy was found over his neck or the axillary and inguinal areas. Digital examination showed nothing abnormal. The following laboratory tests were performed: white blood cell count $9000/mm^3$, hemoglobin 13.5 g/dL, platelet count $257\,000/mm^3$, albumin 4.1 g/dL, aspartate aminotrasferase (AST) 16 U/L, alanine aminotransferase (ALT) 14 U/L, alkaline phosphatase 47 U/L, total bilirubin 0.6 mg/dL, creatinine 0.7 mg/dL, amylase 117 U/L, lipase 48 U/L. Tumor markers, including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9), were also checked and their results were 0.92 ng/mL (normal < 5 ng/mL) and 27.2 U/mL (normal < 37 U/mL), respectively. Then abdominal computed tomography (CT) was performed (Figure 2), which showed two cystic tumors at the level of the pancreatic head and body, measuring 4.8 cm and 1.2 cm, respectively. To further investigate the nature of the tumors, endoscope ultrosonography (EUS) and magnetic resonance imaging (MRI) were carried out. The EUS (Figure 3) disclosed a cystic tumor, 4 cm × 4.2 cm, without obvious internal projective mass in the pancreatic head. The papilla of Vater was grossly normal without mucin discharge. The MRI (Figure 4) showed three cystic lesions in pancreatic head (4.9 cm), body (1.8 cm) and
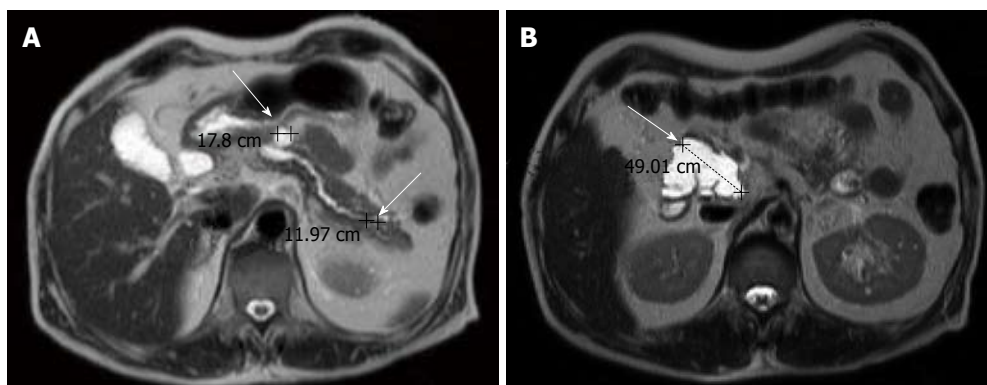
Figure 4 Magnetic resonance imaging showing three cystic lesions in the pancreatic head (4.9 cm), body (1.8 cm) and tail (1.2 cm), with P-duct dilatation. Mild common bile duct and common hepatic duct dilatation without definite tumor was observed in the liver upon MRI.
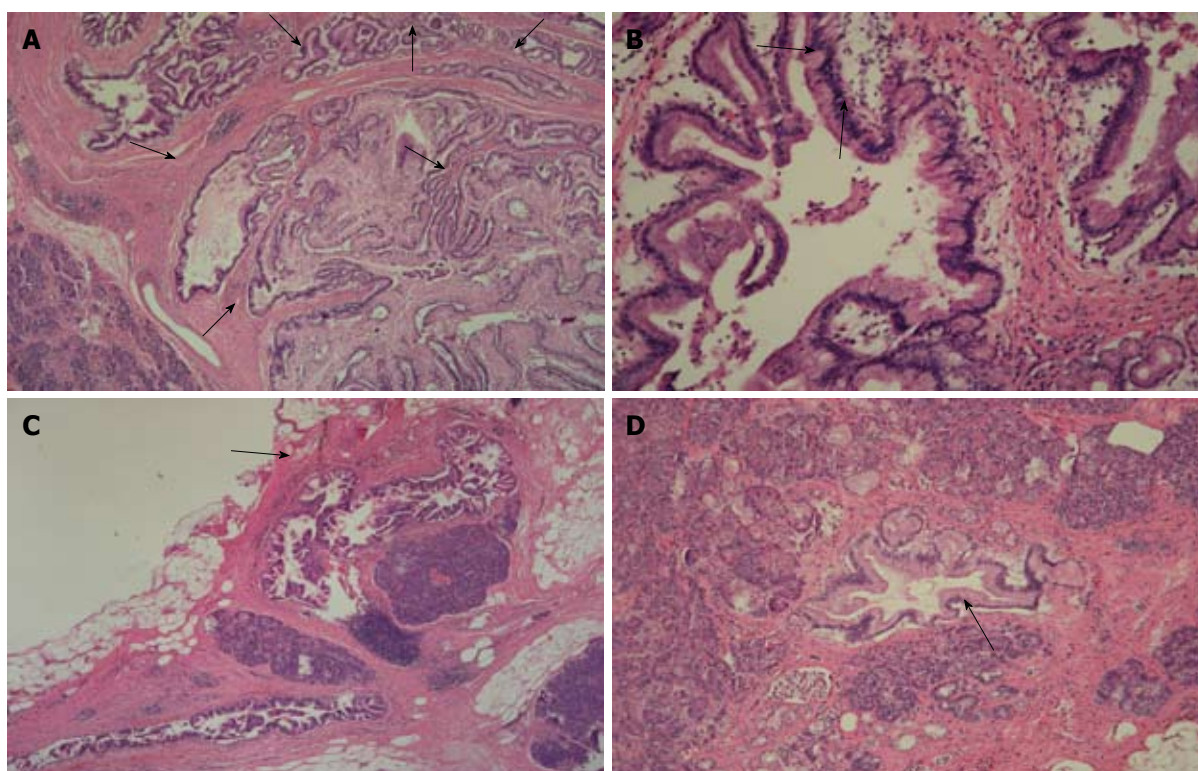

Figure 5 Histopathologic findings (HE × 200). A: Histopathological examination showed the presence of cystically dilated ducts with formation of papillary growth lined by mucin-secreting columnar epithelium at the level of the pancreatic head; B: The mucin-secreting epithelium reveals stratification of atypical nuclei. No obvious stromal invasion was seen and the features suggested a diagnosis of intraductal papillary mucinous carcinoma, noninvasive type; C: The section of the pancreatic body showed that it was focally involved by the lesion (arrow); D: The section of the pancreatic tail showed the focal presence of atypical ducts.

tail (1.2 cm) with pancreatic duct dilatation. Given the presence of pancreas cystic neoplasms, which may be malignant IPMNs, cystic adenocarcinomas or cystic adenomas, affecting the pancreatic head, body and tail, an extended Whipple operation (including the partial resection of the pancreatic body, about 2 cm away from the portal vein) together with a distal pancreatectomy were performed. Intraoperative findings revealed three tumors as described in the MRI. Intraoperative pancreatic US revealed no additional cystic mass in the residual pancreas, measuring about 7 cm in length, after resection. The proximal and distal margins were all negative for malignancy demonstrated by intraoperative histopathologic examination. The regional lymph nodes were grossly normal.

Histopathologic examination revealed that the pancreatic head showed the presence of cystically dilated ducts, encompassing the main and branch ducts, with formation of papillary growth lined by mucin-secreting columnar epithelium. The mucin-secreting epithelium had stratification of atypical nuclei. No obvious stromal invasion was seen. The features suggested a diagnosis of intraductal papillary mucinous carcinoma, non-invasive type (Figure 5A, B). The pancreatic body was focally involved by the lesion (Figure 5C), in the branch duct, not contiguous to the lesion of the pancreatic head. The pancreatic tail displayed focal presence of atypical ducts (Figure 5D), located in the branch duct. The final pathological diagnosis was non invasive mixed (involving both the main and the branch duct) type IPMN (carcinoma *in situ*) in the pancreatic head and branch duct type IPMN (duct atypia) in the body and tail. The postoperative course was uneventful and a three-year disease free survival has been achieved so far.

DISCUSSION

An enormous increase in the diagnosis of IPMN has occurred in recent years[16-18], which is due both to the improvement and widespread use of modern imaging equipments and to a heightened awareness among physicians.

IPMN usually occurs in 60 to 70 years old males, most of whom have a long-standing history of recurrent acute pancreatitis or symptoms suggestive of chronic obstructive pancreatitis, similarly to our patient, due to intermittent obstruction of the pancreatic duct with mucus plugs[19]. Other symptoms are nonspecific[20,21] and no signs or symptoms are pathognomonic of primary cystic neoplasms of the pancreas, including IPMN. Furthermore, many patients with no symptoms have their tumors detected incidentally at imaging studies performed for unrelated indications. Thus, there is often a several months delay in the diagnosis of IPMN, due to the insidious nature of this disease and to the lack of awareness of this entity among physicians[13,20,22-24]. Some patients may have elevations of pancreatic enzymes with episodes of pain (with or without biliary obstruction), but in most cases routine laboratory tests are normal. Similarly, tumor markers, such as CA 19-9 and CEA, are elevated in less than one-fifth of cases only, and are not always indicative of a malignant transformation of the tumors[19]. In this case, there were normal routine laboratory tests and tumor markers.

IPMN is a precancerous lesion with a well described adenoma-carcinoma sequence. However, the rate of progression appears to be extremely slow (approximately 15 to 20 years)[25].

The IPMN has been classified as main duct type (MDT-IPMN) or branch duct type (BDT-IPMN), based upon the anatomic involvement of the pancreatic duct[26,27]. The majority of IPMNs are located in the pancreatic head (75%) whereas the rest involves the body/tail regions[15]. Multifocal neoplasms have been hypothesized[15], but the real prevalence of multifocality is still unknown. The final diagnosis of this case proved the existence of this rare entity.

The majority of patients with IPMN does not have invasive cancer, and usually have a prolonged course without the development of cancer. In one series, the ten-year actuarial risk of high grade dysplasia and invasive cancer were 49% and 29%, respectively[28]. The five-year actuarial risk of progression was significantly higher in patients with main duct type compared with those with exclusively the branch duct type (63% *versus* 15%). Surgery is the only treatment option in patients who do have high grade dysplasia or cancer detected by endoscopic or cytological examination. Preoperative staging, using a combination of ERCP, pancreatoscopy, EUS and intraductal ultrasonography, may be beneficial to determine the indication to surgery[29-32]. However, accurate prediction of malignancy is not possible preoperatively. Sugiyama *et al*[33] proposed some predictive factors of malignant IPMN, including (1) tumor size, since an IPMN > 4 cm and a branch duct IPMN > 3 cm suggest malignancy; (2) a mural nodule of a size > 5 mm; (3) a dilatation of main pancreatic duct > 10 mm; (4) the patient age, the mean age for adenomas being 64, whereas that of invasive cancers is 67; and (5) symptoms, especially jaundice.

Selection of a surgical procedure for treating IPMN remains controversial, because IPMNs show a wide spectrum of histologic changes, ranging from hyperplasia to invasive carcinoma and because of the so far unresolved question of multifocality. As demonstrated in this patient, the aim of surgery is to achieve complete resection with negative margins for invasive and noninvasive disease and to minimize the incidence of recurrence in the pancreatic remnant. However, an extended resection of the pancreas may pose the risk of inducing a severe pancreatic functional insufficiency, both exocrine and endocrine.

Another difficult question is the management of patients with suspected IPMNs who do not have high grade dysplasia or cancer detected during initial evaluation, and of patients with small (< 3 cm) branch-duct IPMNs. Our opinion is that management should be based upon the confidence in the diagnosis, the presence of symptoms and a discussion with the patient regarding the possible risk of subsequent malignant transformation. Surgery can be reasonably offered to patients who are good surgical candidates in order to confirm the diagnosis and to prevent the subsequent development of cancer. In contrast, patients who are poor surgical candidates can be treated conservatively with an imaging test performed every six to twelve months to evaluate the stability of the lesion. Our case fared very well despite the fact that he was 72 years old. Originally, we suggested the resection of pancreatic head with close follow-up of the other two tumors, considering the tiny risk of malignant transformation, but both the patient and his family preferred a complete resection of the three tumors. Finally, we performed an extended Whipple operation (including the partial resection of the pancreatic body) with a distal pancreatectomy. The postoperative course was uneventful without deterioration of the diabetes and exocrine insufficiency.

The final pathologic diagnosis was noninvasive mixed (involving both the main and the branch duct) type IPMN (carcinoma *in situ*) affecting the pancreatic head and a branch duct type IPMN (duct atypia) of the pancreatic body and tail. This confirmed the occurrence of multifocality of IPMNs of the pancreas. The patient has until now achieved a three year disease free survival.

REFERENCES

1   **Becker WF**, Welsh RA, Pratt HS. Cystadenoma and cystadenocarcinoma of the pancreas. *Ann Surg* 1965; **161**: 845-863

2   **Lichtenstein DR**, Carr-Locke DL. Mucin-secreting tumors of the pancreas. *Gastrointest Endosc Clin N Am* 1995; **5**: 237-258

3   **Ohhashi K**, Murakami Y, Takekoshi T. Four cases of mucin producing cancer of pancreas on specific findings of the

papilla of Vater. *Prog Dig Endosc* 1982; **20**: 348-351

4   **Longnecker DS**. Observations on the etiology and pathogenesis of intraductal papillary-mucinous neoplasms of the pancreas. *Hepatogastroenterology* 1998; **45**: 1973-1980

5   **Warshaw AL**. Mucinous cystic tumors and mucinous ductal ectasia of the pancreas. *Gastrointest Endosc* 1991; **37**: 199-201

6   **Nickl NJ**, Lawson JM, Cotton PB. Mucinous pancreatic tumors: ERCP findings. *Gastrointest Endosc* 1991; **37**: 133-138

7   **Itai Y**, Kokubo T, Atomi Y, Kuroda A, Haraguchi Y, Terano A. Mucin-hypersecreting carcinoma of the pancreas. *Radiology* 1987; **165**: 51-55

8   **Shimizu M**, Itoh H, Okumura S, Hashimoto K, Hanioka K, Ohyanagi H, Yamamoto M, Kuroda Y, Tanaka T, Saitoh Y. Papillary hyperplasia of the pancreas. *Hum Pathol* 1989; **20**: 806-807

9   **Morohoshi T**, Kanda M, Asanuma K, Klöppel G. Intraductal papillary neoplasms of the pancreas. A clinicopathologic study of six patients. *Cancer* 1989; **64**: 1329-1335

10   **Kawarada Y**, Yano T, Yamamoto T, Yokoi H, Imai T, Ogura Y, Mizumoto R. Intraductal mucin-producing tumors of the pancreas. *Am J Gastroenterol* 1992; **87**: 634-638

11   **Horvath KD**, Chabot JA. An aggressive resectional approach to cystic neoplasms of the pancreas. *Am J Surg* 1999; **178**: 269-274

12   **Bastid C**, Bernard JP, Sarles H, Payan MJ, Sahel J. Mucinous ductal ectasia of the pancreas: a premalignant disease and a cause of obstructive pancreatitis. *Pancreas* 1991; **6**: 15-22

13   **Yamaguchi K**, Ogawa Y, Chijiiwa K, Tanaka M. Mucin-hypersecreting tumors of the pancreas: assessing the grade of malignancy preoperatively. *Am J Surg* 1996; **171**: 427-431

14   **Kloppel G**, Solcia E, Longnecker DS, Capella C, Sobin LH. Histological typing of tumors of the exocrine pancreas. In: World Health Organization International Histological Classification of Tumours. 2nd ed. Berlin: Springer, 1996: 11-20

15   **D'Angelica M**, Brennan MF, Suriawinata AA, Klimstra D, Conlon KC. Intraductal papillary mucinous neoplasms of the pancreas: an analysis of clinicopathologic features and outcome. *Ann Surg* 2004; **239**: 400-408

16   **Traverso LW**, Peralta EA, Ryan JA Jr, Kozarek RA. Intraductal neoplasms of the pancreas. *Am J Surg* 1998; **175**: 426-432

17   **Loftus EV Jr**, Olivares-Pakzad BA, Batts KP, Adkins MC, Stephens DH, Sarr MG, DiMagno EP. Intraductal papillary-mucinous tumors of the pancreas: clinicopathologic features, outcome, and nomenclature. Members of the Pancreas Clinic, and Pancreatic Surgeons of Mayo Clinic. *Gastroenterology* 1996; **110**: 1909-1918

18   **Sugiyama M**, Atomi Y. Intraductal papillary mucinous tumors of the pancreas: imaging studies and treatment strategies. *Ann Surg* 1998; **228**: 685-691

19   **Bassi C**, Procacci C, Zamboni G, Scarpa A, Cavallini G, Pederzoli P. Intraductal papillary mucinous tumors of the pancreas. Verona University Pancreatic Team. *Int J Pancreatol* 2000; **27**: 181-193

20   **Rivera JA**, Fernández-del Castillo C, Pins M, Compton CC, Lewandrowski KB, Rattner DW, Warshaw AL. Pancreatic mucinous ductal ectasia and intraductal papillary neoplasms. A single malignant clinicopathologic entity. *Ann Surg* 1997; **225**: 637-644; discussion 644-646

21   **Farrell JJ**, Brugge WR. Intraductal papillary mucinous tumor of the pancreas. *Gastrointest Endosc* 2002; **55**: 701-714

22   **Cellier C**, Cuillerier E, Palazzo L, Rickaert F, Flejou JF, Napoleon B, Van Gansbeke D, Bely N, Ponsot P, Partensky C, Cugnenc PH, Barbier JP, Devière J, Cremer M. Intraductal papillary and mucinous tumors of the pancreas: accuracy of preoperative computed tomography, endoscopic retrograde pancreatography and endoscopic ultrasonography, and long-term outcome in a large surgical series. *Gastrointest Endosc* 1998; **47**: 42-49

23   **Obara T**, Saitoh Y, Maguchi H, Ura H, Yokota K, Okamura K, Namiki M. Papillary adenoma of the pancreas with excessive mucin secretion. *Pancreas* 1992; **7**: 114-117

24   **Yamaguchi K**, Chijiiwa K, Shimizu S, Yokohata K, Morisaki T, Yonemasu H, Tanaka M. Intraductal papillary neoplasm of the pancreas: a clinical review of 13 benign and four malignant tumours. *Eur J Surg* 1999; **165**: 223-229

25   **Shimizu Y**, Yasui K, Morimoto T, Torii A, Yamao K, Ohhashi K. Case of intraductal papillary mucinous tumor (noninvasive adenocarcinoma) of the pancreas resected 27 years after onset. *Int J Pancreatol* 1999; **26**: 93-98

26   **Kobari M**, Egawa S, Shibuya K, Shimamura H, Sunamura M, Takeda K, Matsuno S, Furukawa T. Intraductal papillary mucinous tumors of the pancreas comprise 2 clinical subtypes: differences in clinical characteristics and surgical management. *Arch Surg* 1999; **134**: 1131-1136

27   **Terris B**, Ponsot P, Paye F, Hammel P, Sauvanet A, Molas G, Bernades P, Belghiti J, Ruszniewski P, Fléjou JF. Intraductal papillary mucinous tumors of the pancreas confined to secondary ducts show less aggressive pathologic features as compared with those involving the main pancreatic duct. *Am J Surg Pathol* 2000; **24**: 1372-1377

28   **Lévy P**, Jouannaud V, O'Toole D, Couvelard A, Vullierme MP, Palazzo L, Aubert A, Ponsot P, Sauvanet A, Maire F, Hentic O, Hammel P, Ruszniewski P. Natural history of intraductal papillary mucinous tumors of the pancreas: actuarial risk of malignancy. *Clin Gastroenterol Hepatol* 2006; **4**: 460-468

29   **Hara T**, Yamaguchi T, Ishihara T, Tsuyuguchi T, Kondo F, Kato K, Asano T, Saisho H. Diagnosis and patient management of intraductal papillary-mucinous tumor of the pancreas by using peroral pancreatoscopy and intraductal ultrasonography. *Gastroenterology* 2002; **122**: 34-43

30   **Izuishi K**, Nakagohri T, Konishi M, Inoue K, Tajiri H, Kinoshita T. Spatial assessment by magnetic resonance cholangiopancreatography for preoperative imaging in partial pancreatic head resection. *Am J Surg* 2001; **182**: 188-191

31   **Wakabayashi T**, Kawaura Y, Morimoto H, Watanabe K, Toya D, Asada Y, Satomura Y, Watanabe H, Okai T, Sawabu N. Clinical management of intraductal papillary mucinous tumors of the pancreas based on imaging findings. *Pancreas* 2001; **22**: 370-377

32   **Myung SJ**, Kim MH, Lee SK. Pancreatoscopy and magnetic resonance pancreatography may decrease the margin-positive cases and recurrence rate in surgical therapy of mucinous ductal ectasia. *Gastrointest Endosc* 1998; **48**: 556-559

33   **Sugiyama M**, Izumisato Y, Abe N, Masaki T, Mori T, Atomi Y. Predictive factors for malignancy in intraductal papillary-mucinous tumours of the pancreas. *Br J Surg* 2003; **90**: 1244-1249